



Attorney's Docket No.: 13321-001001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shoujun Chen et al. Art Unit : 1615
Serial No. : 10/010,201 Examiner : Robert M. Joynes
Filed : November 30, 2001
Title : METHODS OF USING KAVALACTONE COMPOSITIONS

Commissioner for Patents
Washington, D.C. 20231

RESPONSE

In response to the action mailed July 30, 2002 (the "Action"), Applicants make the following remarks.

Claims 1-35 are pending. Claims 1-35 are rejected. Applicants request consideration of the following remarks.

Rejection under 35 U.S.C. § 103(a)

Claims 1-12 and 27-35 are rejected as unpatentable over Schutt (U.S. Patent 4,248,861) or Rosenbaum (U.S. Patent 5,585,386) in view of Watkins (U.S. Patent 6,159,473), or Watkins, in view of Schutt or Rosenbaum. It is alleged that: (i) Schutt teaches skin compositions having kava kava and that kava kava contains all the kavalactones claimed; (ii) Rosenbaum teaches a topical composition comprising kavain, dihydrokavain, methysticin, dihydromethysticin, and a physiologically acceptable carrier; and (iii) Watkins teaches kava kava as a known topical analgesic. It is then concluded that, based on allegations (i) – (iii), the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Applicants disagree with each of allegations (i) – (iii) above and with the conclusion reached based on those allegations.

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Allegation (i) above fails to accurately convey the Schutt teaching. The Schutt compositions contain 0.5 to 3 parts kava kava extract. Kava kava extract includes a number of various kavalactones, i.e. more than sixteen. Of these, kawain, dihydrokawain, and dihydromethysticin make up about 40% - 60% of the total kavalactone content. Thus, Schutt describes compositions having about 0.006% - 0.4% total content of those three kavalactones. Such compositions are distinguishable from, and are not suggestive of, Applicants' medicinal ointment compositions (i.e., 1% - 90%) used in methods for treating pain.

Applicants have identified three particular kavalactones: kawain, dihydrokawain, and dihydromethysticin, and combinations of them, that provide superior therapeutic effect for IL-12 modulation. See, Specification at page 6, lines 7-11, and Figure 1. This superior and surprising inhibitory effect of a specific single kavalactone (i.e., kawain, dihydrokawain, and dihydromethysticin), or a combination, of kawain, dihydrokawain, and dihydromethysticin in methods of treating pain, was not heretofore recognized. Schutt provides no teaching of any one particular, nor any specific combination (other than the combination of all kavalactones that happen to be in natural extract) of kavalactones. Nor does Schutt suggest pain treatment methods (which is acknowledged in the Action at page 3). The rejection is based on the impermissible use of hindsight upon reading Applicants' disclosure. Neither Schutt, Rosenbaum, nor Watkins provide any motivation to one of ordinary skill at the time of the invention to select one of the three, or a particular combination of kavalactones (i.e., kawain, dihydrokawain, and dihydromethysticin), let alone any particular range of the combination of those three kavalactones, in a medicinal ointment for use in a method for treatment of pain.

Allegation (ii) is a misinterpretation of the Rosenbaum teaching. Rosenbaum, while teaching a topical formulation, fails to teach use of that formulation in a method of treating pain. Moreover, Rosenbaum does not teach any combination of kavalactones, and does not teach the combination of kawain, dihydrokawain, and dihydromethysticin for methods of treating pain (which is acknowledged in the Action at page 3).

The Rosenbaum compositions have at least one α -pyrone compound of a structural formula that describes three variable positions, each having one of five, two, and 24, possible substituents at their respective positions. Thus, a plethora of possible compounds are encompassed by this description. The source of these α -pyrone compounds varies as well. For

example, the α -pyrone compounds are found in piper methysticum (kava kava), Sorbus Aucuparia berries, and Avena Sativa. Thus, these α -pyrone compounds described by Rosenbaum represent a number of compounds that are not kavalactones (i.e., compounds derived from kava kava). Further, Rosenbaum teaches (including for example in claims 2-12) compositions wherein the α -pyrone is one of 11 different α -pyrones. Rosenbaum also discloses one combination of two α -pyrone compounds, and in fact refers to it as "preferred" (see col. 3, lines 17-18); however, that combination is of a kavalactone (kavain) and a compound derived from Avena Sativa (5-methylvalerolactone), which is not a kavalactone. Thus, Rosenbaum does not disclose any particular kavalactone for use in pain treatment methods nor any particular combination of two kavalactones, nor for that matter any combination of more than two kavalactones.

Allegation (iii) is also an overbroad interpretation of the teaching of Watkins. Watkins refers to a sore throat spray. That is, a formulation that is applied to, and absorbed by, mucus membranes. Such a formulation is different from, and its teachings can not be extrapolated to, Applicants' methods using a topical medicinal ointment. The Watkins formulation is made specifically for, and takes advantage of, application to mucus membranes. Such administration routes offer distinctive and differing bioavailability issues compared to Applicants' topical dermal applications. They are distinct and different applications, and one of ordinary skill would not take a teaching in one application and extrapolate it to the other with any reasonable expectation of success. The barrier imposed by mucus membranes is very different from that of the dermis, and as such, formulations for each are different. Thus, Watkins refers to a combination of active ingredients and an administration route that is distinguishable from Applicants' claimed subject matter. There is no teaching or suggestion in Watkins that would lead one of ordinary skill to arrive at Applicants' claimed subject matter, a topical medicinal ointment pain treatment method using one or a combination of specific kavalactones (i.e., kawain, dihydrokawain, and dihydromethysticin), with any reasonable expectation of success.

Applicants note that in the Action, it is stated that neither Schutt nor Rosenbaum expressly teaches that kava kava extracts are used to treat pain. Thus, the assertion in the Action relies on Watkins to provide motivation, in combination with Schutt or Rosenbaum, to arrive at Applicants' claimed subject matter. Watkins fails to do so however. Again, Watkins refers to a

sore throat spray. That is, a formulation that is applied to, and absorbed by, mucus membranes. Such a formulation is different from, and its teachings can not be extrapolated to, Applicants' claimed subject matter, methods of treating pain using a topical medicinal ointment. Thus, Watkins in combination with Schutt or Rosenbaum, or vice versa, does not render Applicants' claimed subject matter obvious.

Based on the foregoing, each of the individual allegations (i) to (iii) in the Action, as well as the conclusion based on them, is flawed and as such, Applicants respectfully request withdrawal of the rejection.

Claims 13-20 are rejected as obvious over Asmussen (U.S. 6,379,696) in view of Elbakyan (WO 00/30578) further in view of Schwabe (U.S. 5,296,224). In the Action, it is alleged that: (i) Asmussen teaches a transdermal therapeutic system comprising kawain; (ii) Elbakyan teaches a transdermal patch composition; (iii) Schwabe teaches kawain and other suitable lactones; and (iv) Watkins teaches that kava kava is a known analgesic. Applicants disagree with these allegations, particularly (iii) and (iv), and the conclusion based on these points.

Asmussen, Elbakyan and Schwabe do not, either alone or in combination, disclose the specific combination of three kavalactones (i.e., kawain, dihydrokawain, and dihydromethysticin), or the specific range by weight of those three components as Applicants have. Asmussen, Elbakyan and Schwabe do not, either alone or in combination, disclose methods of treating pain. This is acknowledged in the Action at page 5. Thus, it is left to Watkins to provide the teaching or suggestion for treating pain.

As delineated above however, Watkins fails to do so. Again, Watkins refers to a sore throat spray. Watkins expressly teaches a specific range of kavalactones (all sixteen as appears in natural extract,) that is distinct from, and provides no teaching or suggestion of, the levels claimed in Applicants' methods (as opposed to Applicants' specific identification of kawain, dihydrokawain, and dihydromethysticin or combination thereof). Again, Watkins refers to a sore throat spray. That is, a formulation that is applied to, and absorbed by, mucus membranes. Such a formulation is different from, and its teachings can not be extrapolated to, Applicants' methods of treating pain using a topical medicinal ointment. Thus, Watkins refers to a

combination of active ingredients and an administration route that is distinguishable from Applicants' claimed subject matter. There is no teaching or suggestion in Watkins that would lead one of ordinary skill to arrive at Applicants' claimed subject matter with any reasonable expectation of success.

Schwabe discloses various kavalactones, including kawain, dihydrokawain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin, but does not provide any motivation to select any particular one or combination thereof. Schwabe also teaches kavalactones in the context of oral bioavailability, which teachings are distinct from, and cannot be extrapolated to, Applicants' topical ointment methods with any reasonable expectation of success. Schwabe does not teach kawain, dihydrokawain, and dihydromethysticin, or a combination thereof for use in methods of treating pain. Schwabe does not teach or suggest the superior activity demonstrated by kawain, dihydrokawain, and dihydromethysticin, or a combination thereof. It is Applicants' that first suggest the desirability and advantages of kawain, dihydrokawain, and dihydromethysticin, or a combination thereof in methods for treating pain.

Neither Asmussen, Elbakyan, Schwabe nor Watkins, alone or in combination, teach or suggest Applicants' claimed subject matter, methods of treating pain using topical ointment compositions having kawain, dihydrokawain, and dihydromethysticin, or a combination thereof. Based on the foregoing, Applicants respectfully request withdrawal of this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

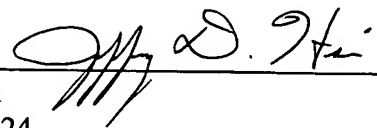
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Applicant asks that all claims be allowed. Enclosed is check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13321-007001.

Respectfully submitted,

Date: January 30, 2003



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